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(54) Title: PRODUCTION OF L-ASCORBIC ACID FROM 2-KETO-L-GULONIC ACID

(57) Abstract

A method for producing *L*-ascorbic acid which comprises (a) forming a substantially anhydrous slurry of 2-keto-*l*-gulonic acid and a surfactant in a supporting organic layer, and (b) reacting said slurry with a substantially anhydrous acid catalyst to convert said 2-keto-*l*-gulonic acid to *L*-ascorbic acid. *L*-ascorbic acid is produced in relatively high yields in a relatively short period of time by converting 2-keto-*l*-gulonic acid to *L*-ascorbic acid by acid catalysis of 2-keto-*l*-gulonic acid under substantially anhydrous conditions.

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PRODUCTION OF L-ASCORBIC ACID FROM 2-KETO-L-GULONIC ACID.

BACKGROUND OF THE INVENTION

1. Field of The Invention

This invention relates to the production of L-ascorbic acid from 2-keto-l-gulonic acid, and, more particularly, to the production of L-ascorbic acid from 2-keto-l-gulonic acid under substantially anhydrous conditions.

2. Description of Related Art

The most successful and common method of producing L-ascorbic acid is based on a multi-step synthesis from d-glucose going through sorbose and 2-keto-l-gulonic acid as described by Reichstein and Grussner, Helv. Chim. Acta., 17, 311-328 (1934). L-ascorbic acid is obtained by heating 2-keto-l-gulonic acid in water at 100°, or by esterifying 2-keto-l-gulonic acid (L-xylo-2-hexulosonic acid), which is in turn converted into L-ascorbic acid by treatment with sodium methoxide in methanol, followed by acidification with hydrogen chloride gas.

A summary of the various techniques for producing L-ascorbic acid is found in Advances in Carbohydrate Chemistry and Biochemistry, Vol. 37, pp. 79-197 (1980).

L-ascorbic acid, aside from its use as a vitamin (Vitamin C), has numerous other industrial and commercial uses.

A Japanese patent publication relating to the production of L-ascorbic acid, 48(1973) - 15931, based on application number 87,371, filed October 5, 1970, is reported in Chemical Abstracts, Vol. 79, 1973, p. 352 (53169Z). This patent publication discloses the preparation of L-ascorbic acid by treating diacetone-2-keto-l-gulonic acid hydrate, 2-keto-l-gulonic acid hydrate, or 2-keto-l-gulonic acid with concentrated hydrochloric acid in the presence of inactive solvents and surfactants. By way of example, this publication discloses heating 100 grams of diacetone-2-keto-l-gulonic acid, 300 ml of benzene, 0.3 grams of stearylpropylenediamine dioleate, and 10 ml of concentrated hydrochloric acid for five hours at 65°C to give 58.7 grams of L-ascorbic acid (purity 97.5%).

None of these publications describe or suggest conducting the single step synthesis of 2-keto-l-gulonic acid to L-ascorbic acid under substantially anhydrous conditions, or that conducting such a reaction under substantially anhydrous conditions substantially decreases the reaction time and substantially increases the total yield of L-ascorbic acid.

SUMMARY OF THE INVENTION

Broadly stated, the present invention contemplates a method for producing L-ascorbic acid by (a) forming a substantially anhydrous slurry of 2-keto-l-gulonic acid and a surfactant in a supporting organic layer, and (b) reacting said slurry with a substantially anhydrous acid catalyst to convert said 2-keto-l-gulonic acid to L-ascorbic acid. A preferred method for producing

L-ascorbic acid utilizes a hydrate of 2-keto-l-gulonic acid.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The general method for producing L-ascorbic acid comprises (a) forming a substantially anhydrous slurry of 2-keto-l-gulonic acid and a surfactant in a supporting layer, and (b) reacting said slurry with a substantially anhydrous acid catalyst to convert said 2-keto-l-gulonic acid to L-ascorbic acid. The one-step synthesis reaction of the present invention will proceed well with essentially no free water added when utilizing a hydrate of 2-keto-l-gulonic acid. However, the reaction of the invention will proceed well with very small amounts of water present such as water present due to processing conditions. Increasing the amount of free water increases reaction time and/or decreases yield. This undesirable effect is due in part to the decomposition of the L-ascorbic acid which takes place in the presence of an aqueous acid.

The 2-keto-l-gulonic acid intermediate can be obtained by a number of well known synthetic routes starting from commercially available L-sorbose. Protection of L-sorbose as a diacetonide can be accomplished in acetone using dimethoxypropane with a sulfuric acid catalyst. The diacetone-l-sorbose can then be oxidized using basic sodium hypochlorite in the presence of a nickel chloride catalyst to give diacetone-2-ketogulonic acid. Removal of the protecting group of the diacetone-2-ketogulonic acid can be accomplished by heating it in distilled water to produce 2-keto-l-gulonic acid.

A convenient method for introducing minimum amounts of water into the reaction is through the use of a hydrate of 2-keto-L-gulonic acid. While 2-keto-L-gulonic acid $1H_2O$ is a true hydrate, further water may be associated with the solid as unbound water. Drying 2-keto-L-gulonic acid in a vacuum at 50°C overnight gives 2-keto-L-gulonic acid nH_2O, where n is a hydrate from about 0 to about 0.5. Air-drying overnight at ambient temperature gives 2-keto-L-gulonic acid nH_2O, where n is a hydrate from about 1 to about 2. A preferred material is produced by drying overnight at ambient temperatures to yield a hydrate of 2-keto-L-gulonic acid nH_2O wherein n is about 1.5. There appears to be a correlation between the hydration state of 2-keto-L-gulonic acid and its conversion to L-ascorbic acid. Generally, as the hydration state of 2-keto-L-gulonic acid decreases, there is a corresponding decrease in its conversion to L-ascorbic acid. It should be noted that the dependence on hydration state is observed under substantially anhydrous (i.e., water starved) conditions. Very small amounts of water can be added to the reaction medium to aid in cyclization; however, no additional water need be added if the hydration state is sufficiently high (e.g., at least about 1.0 and, preferably, about 1.5), providing other reaction criteria are met.

L-ascorbic acid is white crystalline solid melting at 192°C. and having, in water, a specific rotation at the sodium D line of +24°. In solution, L-ascorbic acid has a pK_1 of 4.17 and a pK_2 of 11.79. The more acidic proton has been shown by both chemical and physical methods to be that of the 3-hydroxyl group.

L-ascorbic acid is known to decompose in aqueous acids via a first order reaction with a half life of 5 hours at 70°C. Therefore, minimizing the time that L-ascorbic acid is in contact with aqueous hydrochloric

acid is critical. This is accomplished in the present invention by slurrying the 2-keto-l-gulonic acid in a supporting organic layer and using a minimum amount of water as a reaction medium. The supporting organic layer can be an aromatic solvent, an aliphatic solvent, a halogenated solvent or a mixture thereof. Representative aromatic solvents include toluene, xylene, benzene, ethyl benzene and mixtures thereof. A preferred organic solvent is toluene, either alone or in combination with other organic or aliphatic solvents. Representative aliphatic solvents include hexane, heptane, octane, nonane, decane, dodecane and mixtures thereof. Representative halogenated solvents are dichloromethane, chloroform, carbon tetrachloride and dichloroethane.

Nonionic, cationic and anionic surfactants can be used in this invention; however, nonionic and cationic surfactants are preferred. Examples of surfactants which can be used in the present invention include quaternary ammonium ions, phosphonium ions, amines (which are cationic sources), crown ethers, ethoxylated alcohols, cryptands, aminopolyethers, phosphorylsulfoxides, certain naturally occurring ionophores, glycerol esters, sorbitan esters and mixtures thereof. Representative surfactants include hexadecyltrimethylammonium chloride, oleylamine, tetrabutylammonium chloride, benzyltriethylammonium chloride, trioctylmethylammonium chloride, tricaprylmethylammonium chloride, tetrabutylammonium hydrogen sulfate and mixtures thereof. Typical amounts of surfactants are from about 1 mg to about 250 mg for every gram of 2-keto-l-gulonic acid.

Those skilled in the art will recognize other surfactant materials that are useful in connections with the reaction of the invention. A general listing of surfactants can be found in McCutcheon's Emulsifier & Detergents, 1983 McCutcheon Pub. Co.

The substantially anhydrous acid catalyst can be a mineral acid, or a combination thereof. Representative mineral acids include hydrochloric, sulfuric, nitric, phosphoric and hydrofluoric. A preferred mineral acid is hydrogen chloride gas. The advantages of substantially anhydrous hydrogen chloride gas over other acids are cost, ease of removal from the L-ascorbic acid, low side product formation relative to other mineral acids, and shorter reaction times. In reactions where minute quantities of water are present, such as when the water of hydration of 2-keto-l-gulonic acid serves as the aqueous phase, only enough substantially anhydrous hydrogen chloride gas to saturate this water may be necessary to produce L-ascorbic acid in high yield.

The yield and the purity of the L-ascorbic acid are sensitive to the time and temperature of reaction. The reaction temperature is in the range of from about 40°C to about 80°C. The time of reaction is in the range of from about 2 hours to about 5 hours. In general, lower reaction temperatures give poorer conversions requiring longer reaction times. In general, higher temperatures give acceptable conversions but lower crude yields (decomposition may occur). A preferred reaction time is from about 2 hours to about 4 hours. A preferred reaction temperature is from about 60°C to about 70°C. A reaction time of about 3 hours at a temperature of about 65°C produces high crude yields of L-ascorbic acid. The reaction can, of course, be conducted at atmospheric or superatmospheric pressure.

Since the reaction of the invention proceeds best in substantially anhydrous conditions, it is carried out by including the 2-keto-l-gulonic acid (hydrate) in a slurry and bubbling hydrogen chloride gas through the slurry. Aqueous HCl is not used due to the decomposition of L-ascorbic acid it causes. However, small amounts of

concentrated HCl can be used to facilitate the reaction. The materials used to form the slurry and thus aid in promoting the reactions of the invention may vary substantially depending on factors such as the end use the L-ascorbic acid will be put to, (e.g., industrial, pharmaceutical, etc.). Accordingly, different materials may be used depending on economic and purity requirements. Depending on the ultimate application of the L-ascorbic acid, it will, of course be necessary to use materials (e.g., solvents, surfactants, reaction intermediates, etc.) which comply with various state, federal or foreign regulations.

The aforesaid invention is illustrated by the following specific examples

EXAMPLE 1

L-ascorbic acid

Into a 25 ml, 3-neck flask is placed 20 ml of toluene and 50 mg of hexadecyltrimethylammonium chloride. The solution is heated to 65°C and 5.0 gms, 0.023 moles of 2-keto-l-gulonic acid (1.5 hydrate) is added all at once which forms a slurry. Hydrogen chloride gas is bubbled in at a rate of 80 ml/min. for 3 hours. The toluene is then removed by rotary evaporation under reduced pressure at 30°C. The solid is diluted with 20 ml of toluene and again evaporated to ensure all water is removed. The solid is washed 2 times with toluene and dried under vacuum overnight. The yield is 4.18 gms, 0.0226 moles, 99%, of the tan, 1/2 hydrate of L-ascorbic acid. m.p. = 184-187°C; 93/0 wt% L-ascorbic acid/2-keto-l-gulonic (by high pressure liquid chromatography) $[a]^{25}$ = +47.8° (c=1 in methanol).

EXAMPLE 2

L-ascorbic acid

Into a 25 ml, 3-neck flask is placed 20 ml of toluene and 50 mg of hexadecyltrimethylammonium chloride. The solution is heated to 65°C and 5.0 gms of 2-keto-l-gulonic acid (1.5 hydrate) is added, followed immediately by 1.0 ml of concentrated HCl. Following this, HCl gas is blown through the slurry at a rate of 80 ml/minute for 2.5 hours. The toluene is removed at 30°C under reduced pressure. This step is repeated twice to ensure dryness. The light brown solid is dried in vacuum overnight. The yield is 4.32 gms., 0.0213 moles, 94%; m.p. = 180-184°C; 90/1 wt% L-ascorbic acid/2-keto-l-gulonic acid (by high pressure liquid chromatography).

EXAMPLE 3

L-ascorbic acid

Into a 25 ml, 3-neck flask is placed 20 ml of toluene, 1 ml of distilled water and 50 mg of hexadecyltrimethylammonium chloride. The mixture is heated to 65°C and 5.0 gms of 2-keto-l-gulonic acid (1.5 hydrate) is added all at once. With stirring, hydrogen chloride gas is bubbled through the solution for 5 hours. After cooling to 30°C toluene is removed by rotary evaporation at reduced pressure. After adding additional toluene and removing it two additional times, the tan solid is dried. The yield is 4.32 gms, 0.0213 moles, 94%, m.p. = 181-185°C; 85/1 wt% L-ascorbic acid/2-keto-l-gulonic acid (by high pressure liquid chromotography).

EXAMPLE 4

Purification L-ascorbic acid

Into a 50 ml, 3-neck roundbottom flask is placed 20 ml of distilled water. The crude ascorbic acid, 2.0 gms is dissolved into the water at room temperature and 0.2 gms of decolorizing charcoal is added. The slurry is filtered through diatomaceous earth and the filter cake washed with 5 ml of water. The water is removed by rotary evaporation and the white solid is washed with toluene and dried in a vacuum oven. The yield is 1.90 gms of L-ascorbic acid; m.p. = 180-181°C.

The purification procedure used varies depending on factors such as the materials used to form the slurry (e.g., toxic, non-toxic), the desired end use of the L-ascorbic acid (e.g., industrial, pharmaceutical) availability of materials, time and economics.

The present invention has been disclosed and described herein with the inclusion of specific embodiments. However, the scope of the invention is limited only by the claims and not specific embodiments.

IN THE CLAIMS

1. A method for producing L-ascorbic acid comprising:

(a) forming a substantially anhydrous slurry of 2-keto-l-gulonic acid and a surfactant in a supporting organic layer; and

(b) reacting said slurry with a substantially anhydrous acid catalyst to convert said 2-keto-l-gulonic acid to L-ascorbic acid.

2. A method according to Claim 1, wherein said 2-keto-l-gulonic acid is a hydrate.

3. A method according to Claim 2, wherein said hydrate is 2-keto-l-gulonic acid nH_2O wherein n is from about 0.1 to about 2.0.

4. A method according to Claim 2, wherein said hydrate is 2-keto-l-gulonic acid nH_2O wherein n is from about 1.0 to about 1.75.

5. A method according to Claim 2, wherein said hydrate is 2-keto-l-gulonic acid nH_2O wherein n is about 1.5.

6. A method according to Claim 1, wherein said surfactant is selected from the group consisting of quarternary ammonium ions, phosphonium ions, amines, crown ethers, cryptands, aminophosphorylsulfoxides, ionophores, glycerol esters, ethoxylated alcohols, sorbitan esters and mixtures thereof.

7. A method according to Claim 6, wherein said surfactant is selected from the group consisting of

quarternary ammonium halides, glycerol esters and mixtures thereof.

8. A method according to Claim 6, wherein said surfactant is selected from the group consisting of glycerol esters and mixtures thereof.

9. A method according to Claim 1, wherein said supporting layer is selected from the group consisting of aromatic solvents, aliphatic solvents and mixtures thereof.

10. A method according to Claim 9, wherein said supporting layer is selected from the group consisting of toluene, xylene, hexane, heptane, octane, nonane, decane and mixtures thereof.

11. A method according to Claim 9, wherein said supporting layer is toluene.

12. A method according to Claim 1, wherein said acid catalyst is selected from the group consisting of mineral acids and mixtures thereof.

13. A method according to Claim 12, wherein said acid catalyst is gaseous hydrogen chloride.

14. A method according to Claim 1, wherein said substantially anhydrous slurry contains water as only the water of hydration of 2-keto-l-gulonic acid.

15. A method according to Claim 1, wherein reacting the slurry to convert 2-keto-l-gulonic acid to L-ascorbic acid takes from about 1 to about 5 hours.

16. A method according to Claim 15, wherein reacting the slurry to convert 2-keto-L-gulonic acid to L-ascorbic acid takes about 2 to about 4 hours.

17. A method according to Claim 1, wherein the L-ascorbic acid is produced in a yield of greater than 90%.

18. A method according to Claim 17, wherein the L-ascorbic acid is produced in a yield of greater than 93%.

19. A method according to Claim 1, wherein said L-ascorbic acid has a substantially light gray or light tan color.

20. A method according to Claim 1, wherein the L-ascorbic acid is produced at superatmospheric pressure.

21. A method according to Claim 1, wherein said 2-keto-L-gulonic acid is a hydrate, said supporting organic layer is an aromatic solvent and said acid catalyst is a mineral acid.

22. A method according to Claim 21, wherein said hydrate of 2-keto-L-gulonic acid has a hydration state of about 1.5.

23. A method according to Claim 21, wherein said aromatic solvent is toluene.

24. A method according to Claim 21, wherein said mineral acid is gaseous hydrogen chloride.

25. A method according to Claim 21, wherein said surfactant is a glycerol ester.

26. A method according to Claim 21, wherein said hydrate of 2-keto-L-gulonic acid has a hydration state of about 1.5, said aromatic solvent is toluene, said mineral acid is gaseous hydrochloric acid, and said surfactant is a sorbitan ester.

27. L-ascorbic acid made by the process of Claims 1 to 26.

28. Converting 2-keto-L-gulonic acid to L-ascorbic acid by acid catalysis of 2-keto-L-gulonic acid under substantially anhydrous conditions.

29. Converting 2-keto-L-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 28, wherein the 2-keto-L-gulonic acid is formed into a substantially anhydrous slurry and the slurry is brought into contact with a substantially anhydrous acid catalyst.

30. Converting 2-keto-L-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 29, wherein the slurry is comprised of 2-keto-L-gulonic acid and a surfactant in a supporting organic layer.

31. Converting 2-keto-L-gulonic acid to L-ascorbic acid in the manner as claimed in Claim 28, wherein the 2-keto-L-gulonic acid is a hydrate.

32. Converting 2-keto-L-gulonic acid to L-ascorbic acid in the manner as claimed in Claim 31, wherein the hydrate is 2-keto-L-gulonic acid nH_2O wherein n is from about 0.1 to about 2.0.

33. Converting 2-keto-L-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 32, wherein the hydrate n is in the range of from about 1.0 to about 1.75.

34. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 33, wherein the n is about 1.5.

35. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 28, wherein the acid catalyst is essentially comprised of gaseous hydrogen chloride.

36. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 29, wherein the substantially anhydrous slurry contains water as only the water of hydration of 2-keto-l-gulonic acid.

37. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 28, wherein the converting is carried out for a period of time of about 1 to about 5 hours.

38. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 37, wherein the converting is carried out over a period of time of about 2 to about 4 hours.

39. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 28, wherein the yield of L-ascorbic acid is greater than 90%.

40. Converting 2-keto-l-gulonic acid to L-ascorbic acid in a manner as claimed in Claim 39, wherein the yield of L-ascorbic acid is greater than 93%.

AMENDED CLAIMS
[received by the International Bureau on 29 January 1987 (29.01.87);
original claims 1-40 replaced by new claims 1-23 (3 pages)]

1. A method for producing L-ascorbic acid comprising:

(a) forming a substantially anhydrous slurry of 2-keto-l-gulonic acid and a surfactant in a supporting organic layer; and

(b) reacting said slurry with substantially anhydrous hydrogen chloride gas acid catalyst at a temperature from about 40°C to about 80°C for about 2 to about 5 hours to convert said 2-keto-l-gulonic acid to L-ascorbic acid.

2. A method according to Claim 1, wherein said 2-keto-l-gulonic acid is a hydrate.

3. A method according to Claim 2, wherein said hydrate is 2-keto-l-gulonic acid . nH_2O wherein n is from about 0.1 to about 2.0.

4. A method according to Claim 2, wherein said hydrate is 2-keto-l-gulonic acid . nH_2O wherein n is from about 1.0 to about 1.75.

5. A method according to Claim 2, wherein said hydrate is 2-keto-l-gulonic acid . nH^2O wherein n is about 1.5.

6. A method according to Claim 1, wherein said surfactant is selected from the group consisting of quarternary ammonium ions, phosphonium ions, amines, crown ethers, cryptands, aminophosphorylsulfoxides, ionophores, glycerol esters, ethoxylated alcohols, sorbitan esters and mixtures thereof.

7. A method according to Claim 6, wherein said surfactant is selected from the group consisting of quarternary ammonium halides, glycerol esters and mixtures thereof.

8. A method according to Claim 6, wherein said surfactant is selected from the group consisting of glycerol esters and mixtures thereof.

9. A method according to Claim 1, wherein said supporting layer is selected from the group consisting of aromatic solvents, aliphatic solvents and mixtures thereof.

10. A method according to Claim 9, wherein said supporting layer is selected from the group consisting of toluene, xylene, hexane, heptane, octane, nonane, decane and mixtures thereof.

11. A method according to Claim 9, wherein said supporting layer is toluene.

12. A method according to Claim 1, wherein said acid catalyst consists of gaseous hydrogen chloride.

13. A method according to Claim 1, wherein said substantially anhydrous slurry contains water as only the water hydration of 2-keto-l-gulonic acid.

14. A method according to Claim 1, wherein reacting the slurry to convert 2-keto-L-gulonic acid to L-ascorbic acid takes about 2 to about 4 hours.

15. A method according to Claim 1, wherein the L-ascorbic acid is produced in a yield of greater than 90%.

16. A method according to Claim 15, wherein the L-ascorbic acid is produced in a yield of greater than 93%.

17. A method according to Claim 1, wherein said L-ascorbic acid has a substantially light gray or light tan color.

18. A method according to Claim 1, wherein the L-ascorbic acid is produced at a superatmospheric pressure.

19. A method according to Claim 1, wherein said 2-keto-L-gulonic acid is a hydrate and said supporting organic layer is an aromatic solvent.

20. A method according to Claim 19, wherein said hydrate of 2-keto-L-gulonic acid has a hydration state of about 1.5.

21. A method according to Claim 20, wherein said aromatic solvent is toluene.

22. A method according to Claim 19, wherein said surfactant is a glycerol ester.

23. A method according to Claim 19, wherein said hydrate of 2-keto-L-gulonic acid has a hydration of about 1.5, said aromatic solvent is toluene, said mineral acid is gaseous hydrochloric acid, and said surfactant is a sorbitan ester.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 86/01620

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 307/62

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 307/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Chemical Abstracts, volume 79, no. 9, 3 September 1979, (Columbus, Ohio, US), see page 352, abstract no. 53169z, & JP, A, 7315931 (Takeda Chemical Industries) (18 May 1973) (cited in the application)	1-40
A	CH, A, 187934 (HOFFMANN-LA ROCHE) 1 March 1937 see the whole document	1-40
A	EP, A, 0091134 (SHIONOGI & CO.) 12 October 1983 see the whole document	1-40

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
3rd November 1986	10 DEC 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	L. ROSSI

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 86/01620 (SA 14227)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/11/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A- 187934		None	
EP-A- 0091134	12/10/83	GB-A,B 2118187	26/10/83
		JP-A- 58177986	18/10/83
		US-A- 4491668	01/01/85